Refer to: Wilson MG, Gilman JA, Kellogg B: Prenatal diagnosis by amniocentesis in 800 pregnancies. West J Med 131: 201-204, Sep 1979

Prenatal Diagnosis by Amniocentesis in 800 Pregnancies

MIRIAM G. WILSON, MD; JUNE A. GILMAN, MS, *and* BONNIE KELLOGG, MS, *Los Angeles*

Prenatal diagnoses by amniocentesis have been made in 800 pregnancies at the Genetics Division of the Los Angeles County-University of Southern California Medical Center. This experience has indicated that the amniocentesis procedure is safe and highly accurate. Amniocentesis was not associated with significant morbidity or mortality for either infant or mother. The observed complications are assumed to be related to the high-risk nature of these pregnancies, the patients having been selected primarily on the basis of advanced maternal age or a previous abnormal child. The needle puncture marks, which occurred in 2.4 percent of the live births, resulted in no serious developmental or cosmetic effects to the infants. No errors in cytogenetic diagnosis are known to have occurred in this series.

BETWEEN 1969 AND 1978 the Genetics Division of the Los Angeles County-University of Southern California (LAC-USC) Medical Center completed laboratory analyses of specimens of 800 amniocenteses done for prenatal diagnosis. The total number of women referred for amniocentesis was 1,099.

Referrals

Most referrals were made to check for possible fetal chromosomal abnormality. The reasons given most frequently for referral were the following: advanced maternal age of 35 years or more (65.9 percent), a previous child with a chromosomal abnormality, usually the Down syndrome (16.2 percent) and a family history of the Down syndrome or other chromosomal abnormality (3.4 percent) (Table 1). Of the referrals, 11 (1 percent) were for a parental carrier of a chromosomal translocation or inversion as identified by a previous birth of an affected child, a family chromosomal study in three instances and a history of four abortions in another instance. Two of these families were reported previously.[1,2] In 5.5 percent of the referrals, the parents were anxious because of a family history of nonspecific mental retardation or congenital defects.

A substantial number of women were referred because of an increased risk for a fetus with a neural tube defect. Of the referrals, 6.3 percent were for the detection of a fetal neural defect because of a previously affected child, an affected parent or other family history. A smaller number of referrals was for detectable metabolic disorders and determining the sex of the fetus for X-linked disorders.

Of the 1,099 women referred for prenatal diag-

From the Genetics Division, Department of Pediatrics, University of Southern California School of Medicine and Los Angeles County-USC Medical Center, Los Angeles.

Funds for this study were provided by Public Health Service grant #286 from Maternal and Child Health Services, The National Foundation—March of Dimes, and Maternal and Child Health Services of the State of California.

Submitted, revised, May 14, 1979.

Reprint requests to: Miriam G. Wilson, MD, Genetics Division, Department of Pediatrics, LAC-USC Medical Center, 1129 North State Street, 1G-24 General Laboratories Building, Los Angeles, CA 90033.

ABBREVIATIONS USED IN TEXT
AFP = alpha-fetoprotein
LAC-USC Medical Center = Los Angeles County-University of Southern California Medical Center

nosis, 299 (27.2 percent) either decided not to have or did not have amniocentesis (Table 2). The most common reasons for not having amniocentesis were as follows: (1) concern about the safety of the procedure, (2) alleviation of parental anxiety by counseling and, in some instances, by information obtained through ultrasonographic testing, (3) a spontaneous abortion before the procedure, (4) election of a medical abortion without amniocentesis, (5) an erroneous diagnosis of pregnancy, (6) pregnancy too far advanced for amniocentesis and (7) a decision not to find out whether the fetus was abnormal. In 36 instances there was no indication for amniocentesis. Over the years, there has been a decrease in the proportion of patients who have decided not to have amniocentesis from 30 percent for the years before 1975 to 22 percent for 1978. A small proportion of older women in our population may not accept amniocentesis, possibly for cultural or religious reasons.

More than half of the referrals were from private physicians (59.8 percent), indicating that prenatal diagnosis is used primarily by women in the private sector. The self-referred patients (13.4 percent), were usually those who had had previous genetic counseling or prenatal diagnosis at the LAC-USC Genetics Division. Other referral sources were the Los Angeles County Health Department (9.4 percent), LAC-USC Medical Center (8.8 percent) and other hospitals (7.8 percent). A small number were from Regional Centers for the Developmentally Disabled (0.7 percent) and the National Foundation—March of Dimes (0.1 percent).

Laboratory Procedures

Fetal karyotyping using special banding patterns as needed, was done when the fetus was at increased risk for chromosomal abnormalities. Karyotyping was also done for fetal sex determination for nondetectable X-linked disorders. In addition

TABLE 1.—*1,099 Referrals for Amniocentesis by Indication*

Indication	*Amniocentesis Done*	*Amniocentesis Not Done*	*Subtotal (Percent)*	*Total (Percent)*
Chromosomal				1,011 (92.0)
Older maternal age			724 (65.9)	
Maternal age less than 35 years*	25	9		
Maternal age 35 to 39 years	361	112		
Maternal age more than 39 years	167	50		
Previous child with chromosomal abnormality			178 (16.2)	
Maternal age less than 35 years	111	30		
Maternal age 35 to 39 years	23	4		
Maternal age more than 39 years	8	2		
Parental carrier of chromosomal abnormality			11 (1.0)	
Maternal age less than 35 years	8	2		
Maternal age 35 to 39 years	1	..		
Maternal age more than 39 years	..	..		
Family history of chromosomal abnormality†	15	23	38 (3.4)	
Other (anxiety)†	21	39	60 (5.5)	
X-linked disease†	4	5		9 (0.8)
Inborn metabolic error†	9	1		10 (0.9)
Neural tube defect				69 (6.3)
Previous affected child			62 (5.6)	
Maternal age less than 35 years	43	15		
Maternal age 35 to 39 years	2	2		
Maternal age more than 39 years	..	..		
Affected parent†	2	1	3 (0.3)	
Family history†	..	4	4 (0.4)	
TOTAL	800	299		1,099 (100.0)

*Including maternal age 35 years at expected date of delivery.
†Maternal age less than 35 years.

to the chromosome analysis, ultrasonographic studies and alpha-fetoprotein (AFP) determinations from amniotic fluid were made in most instances.

Ultrasonography is carried out for two reasons: to identify the position of the placenta so that the safest site may be located for the amniocentesis tap, and to identify twins or gross fetal anomalies. AFP determinations are made to measure increased AFP levels, which may provide information about the presence of a fetal neural tube defect. Ultrasonographic testing and AFP measurement are now done routinely at the LAC-USC Medical Center in all instances of diagnostic amniocentesis in midpregnancy.

When the indication was increased risk for fetal metabolic disease, enzyme analysis of cultured amniotic fluid cells was used to identify the specific metabolic disease. When the indication was increased risk for fetal neural tube defect, an ultrasonographic study was carried out and AFP determined. Regardless of the specific indication, chromosome analysis was always done from cultures of amniotic fluid cells.

TABLE 2.—*Reasons for Not Doing Amniocentesis in 299 Referrals*

	Number
Procedure Indicated But Not Done	
Did not want risk of abortion or fetal injury	69
Believed risk of having abnormal child not great	31
Had spontaneous abortion before procedure	23
Opposed to medical abortion if abnormal fetus found	14
Elected medical abortion without amniocentesis	12
Decided to have ultrasound test only	9
Referred elsewhere	8
Frightened of procedure	8
Found not to be pregnant	7
Had medical complications during the pregnancy	7
Was too advanced in pregnancy	6
Wanted information not provided by procedure	6
Was tapped but no fluid obtained	6
Had twin pregnancy (anatomically difficult)	1
Decided against (inconvenient)	2
Decided against (reason unknown)	54
Procedure Not Indicated	36
TOTAL (27.2 percent of referrals)	299

Results

Results from amniocentesis are found in Table 3. Of the 800 amniocenteses, 16 (2 percent) showed abnormal chromosomal constitutions. Of these, 4 were balanced structural rearrangements and 12 were unbalanced with confirmed abnormal phenotypes, and one fetus that showed trisomy 21 was aborted spontaneously and not examined.

The National Institutes of Health (NIH) Collaborative Study reported 2 percent aneuploid fetuses by maternal age category equal to or greater than 35 years.[3] In mothers 35 years or older, the Down syndrome (trisomy 21) occurred in one (0.6 percent) of the fetuses. In the experience of the LAC-USC Genetics Division, of the 587 mothers 35 years of age or older, aneuploidy occurred in nine (1.5 percent) and the Down syndrome (trisomy 21) occurred in five (0.9 percent) of the fetuses.

Of the 412 women 35 to 39 years of age studied by amniocentesis at the LAC-USC Genetics Division, three (0.7 percent) were found to have fetuses with trisomy 21. Of the 167 women 40 to 44 years of age, one (0.6 percent) had a fetus with trisomy 21. Carter and Evans[4] found that 0.4 percent of the women 35 to 39 years old, 1.0 percent of the women 40 to 44 years old and 2.0 percent of the women 45 to 49 years old had infants with the Down syndrome.

Of the four fetuses in whom the sex was determined because of a possible X-linked disorder, all were found to be male. Two were at risk for Duchenne muscular dystrophy and were aborted, one medically and the other spontaneously. The muscle tissue from both of these males was examined by electron microscopy and found to have changes consistent with the disorder. The other

TABLE 3.—*Fetal Abnormalities Found in 800 Pregnancies*

Indication	*Fetal Abnormality*					*Number*
Chromosomal	*Aneuploidy*					
	+21	+18	+18,XXY	+13	XXX	
Maternal age						
35 to 39 years	3	..	1	1	..	5
40 to 44 years	1	1	..	..	1	3
More than 44 years	1	..	..	..	..	1
Parental carrier of inversion or translocation	Abnormal (unbalanced)					3
	Carrier (balanced)					4
Inborn metabolic error	Pompe disease					2
X-linked disorder (for fetal sex determination)	Male sex					4

TABLE 4.—*Outcomes of 800 Pregnancies with Second Trimester Amniocentesis*

	Number	Percent
Single infant of normal weight*	620	77.5
Set of twins†	9	1.1
Single infant of low birth weight (2,500 grams or less)‡	65	8.1
Fetal death before 28 weeks§	15	1.9
Medical abortion (for abnormal fetus)	14	1.8
Medical abortion (other)	5	0.6
Fetal death after 28 weeks	7	0.9
Pending delivery	36	4.5
Lost to follow-up	29	3.6
TOTAL	800	100.0

*1 neonatal death.
†12 of 18 infants were of low birth weight; 2 neonatal deaths.
‡7 neonatal deaths.
§12 fetal deaths occurred within one month of the procedure.

two male fetuses were at risk for X-linked hydrocephaly. One fetus was medically aborted and appeared normal. The other was carried to term, and was born with hydrocephaly.

The outcomes of pregnancy in the 800 women who had amniocentesis are presented in Table 4. No discrepancies occurred between the laboratory diagnosis of the chromosomal sex and the phenotypic sex. All fetuses diagnosed as chromosomally unbalanced or biochemically abnormal were aborted electively with two exceptions: a fetus with triplo-X that the parents decided not to abort and a fetus with trisomy 21 that was spontaneously aborted at home and not examined. Other prenatal chromosomal abnormalities were confirmed by observation of phenotype and repeat chromosome analysis after abortion. However, specimens from one fetus with clinical evidence of the Down syndrome and one fetus that showed the trisomy 18 syndrome were not successfully cultured a second time due to failure of growth from abortus tissue.

Of the 22 fetal deaths during the pregnancies, 12 occurred within one month after amniocentesis, representing a 1.6 percent fetal loss in the 752 women at risk. (Women who had medical abortions or who were lost to follow-up were not included in these calculations.) An additional three women aborted spontaneously after one month but before 28 weeks of pregnancy. The fetal deaths that occurred after amniocentesis represent a 2 percent rate of fetal loss. In addition, there were 23 women who were scheduled for amniocentesis but who aborted before the procedure. The total fetal loss rate before and after amniocentesis, therefore, was 3.6 percent. Both of these rates (2.0 percent and 3.6 percent) are less than the rate reported by Stein and associates[5] for women at comparable stages in pregnancy. Amniocentesis does not appear to increase the risk of spontaneous abortion.

Five sets of parents decided on medical abortion even though amniocentesis gave normal results. The indications for amniocentesis in these cases were advanced maternal age in four and a previous child with a neural tube defect in the fifth. Three of the fetuses were aborted because of their sex, and two were aborted for psychosocial reasons (out-of-wedlock pregnancies).

So far, 703 infants have been born alive. Of these, 77 (11.0 percent) were of low birth weight (2,500 grams or less). There were ten neonatal deaths, nine of which were related to low birth weight (Table 4). One of these low-birth-weight infants also had bilateral polycystic renal disease. The tenth neonatal death occurred in a term infant due to meconium aspiration pneumonia. Needle puncture marks were found in 17 infants, 2.4 percent of all live births. These marks were not significant in terms of fetal development or cosmetic importance.[6] Other congenital abnormalities, usually minor, occurred in 35 infants. None of these abnormalities had any apparent relationship to the procedure of amniocentesis.

Follow-up of Infants

In children born to women who had amniocentesis, follow-up studies are being done routinely for three or more years to assess physical and developmental status. These studies include a physical examination and a developmental assessment by the Gesell testing technique when the infant is 9 months old, and a complete physical and psychometric evaluation at 3 years. No serious physical or developmental problems have been found in any of the 427 children in whom studies have been done.

REFERENCES

1. Ebbin AJ, Wilson MG, Towner JW, et al: Prenatal diagnosis of an inherited translocation between chromosomes No. 9 and 18. J Med Genet 10:65-69, 1973

2. Fujimoto A, Towner JW, Turkel SB, et al: A fetus with recombinant chromosome 8 inherited from her carrier father. Hum Genet 40:241-248, 1978

3. The safety and accuracy of mid-trimester amniocentesis, USDHEW Pub No (NIH) 78-190. US Department of Health, Education, and Welfare, 1978

4. Carter CO, Evans KA: Risk of parents who have had one child with Down's syndrome (mongolism) having another child similarly affected. Lancet 2:785-788, 1961

5. Stein Z, Susser M, Guterman AV: Screening programme for prevention of Down's syndrome. Lancet 1:305-310, 1973

6. Broome DL, Wilson MG, Weiss B, et al: Needle puncture of fetus: A complication of second-trimester amniocentesis. Am J Obstet Gynecol 126:247-252, 1976